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(54) Title: TROPYL 7-AZAINDOL-3-YLCARBOXYAMIDES AS ANTITUSSIVE AGENT


(57) Abstract

Optionally substituted pharmacologically active tropyl 7-azaindol-3-ylcarboxamides and their possible correspondent oxides, the process for their preparation and the pharmaceutical compositions containing them are described.

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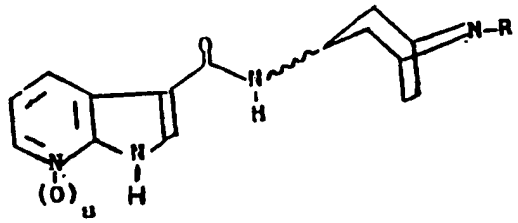
Description

# TROPYL 7-AZAINDOL-3-YLCARBOXYAMIDES AS ANTITUSSIVE AGENT

The present invention refers to tropyl 7-azaindol-3-ylcarboxyamides of formula (I)



(I)

wherein the symbol ⟋⟍ indicates that compounds (I) may have the configuration exo(or β-) or endo(or α-) and

R represents a hydrogen atom; a saturated linear or branched $C_1$-$C_4$ alkyl; a $C_7$-$C_9$ arylalkyl; a $-(CH_2)_n-(C_3-C_7)$ cycloalkyl group wherein n is an number between 0 and 4; a $C_1$-$C_{12}$ acyl group,

s repreents 0 or 1.

As $C_3$-$C_7$ membered cycloaliphatic ring cyclopropyl, cyclopentyl and cyclohexyl are preferred.

As $C_7$-$C_9$ arylalkyl the benzyl and the phenethyl radical are preferred.

As $-(CH_2)n-(C_3-C_7)$ cycloalkyl group, the cyclopropylmethyl group is preferred.

As $C_1$-$C_{12}$ acyl group the formyl group is preferred.

Among $C_1$-$C_4$ alkyl radicals are preferred the methyl, ethyl and isopropyl radicals.

A further object of the invention is represented by the compounds of formula (I) wherein the aminotropyl group is protected by a suitable conventional protecting group among which is preferred the ter-butoxycarbonyl. Also included in the sc pe of the invention are the acid addition salts of the

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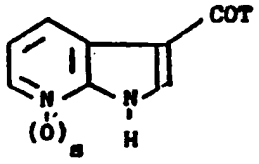
compounds (I) with suitable, non-toxic, pharmaceutically acceptable acids. Among these salts are cited the hydrochorides, hydrobromides, alkyl and arylsulfonates, succinates, tartrates and citrates.

The compounds of formula (I) are obtained by reaction of a tropylamine of formula (III):

(III)

wherein the symbols R and ~~ have the above defined meaning, with an optionally activated azaindolyl-3-carboxylic acid (IV):



(IV)

wherein the sywbol s, has the above mentioned meaning and T represents a hydroxy group or the residue of a carboxylic acid activating group. Preferred activating groups are those well known in the art such as, for example, chorine, bromine, azide, imidazolide, — p-nitrophenoxy, 1-benzotriazole, N-O-succinimide, acyloxy and more specifically, pivaloyloxy, C1-C4 alkoxycarbonyloxy, such as, for example, $C_2H_5OCO-O-$, a dialkyl- or a dicycloalkyl-O-ureide. The carboxyamides of formula (I) are isolated from the reaction mixture as free bases r as addition compounds with a suitable mineral or rganic acid. When the compounds of formula (IV) are used in

th ir fre acid form, th reaction is carried out in the presence of a condensing agent such as, for example, a carbodiimide, optionally in the presence of an activating agent such as, for example, hydroxybenzotriazole or hydroxysuccinimide, with the intermediate formation of dialkyl- or dicycloalkyl-O-ureides. Typical condensing agents are the dicyclohexyl- and the diisopropylcarbodiimide, carbodiimides soluble in an aqueous medium etc. Preferred reaction conditions are those which provide the use of equimolar amounts of the reagents, in inert solvents such as ethyl acetate, aromatic hydrocarbons such as benzene and toluene, cycloalkanes such as cyclohexane, dioxane, tetrahydrofuran, dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, acetonitrile and the mixtures thereof, operating at a temperature between room temperature and the reflux temperature of the mixture, preferably at 50-60°C.

The bicyclic tropylamines (III) are generally well known and also commercially available compounds. They may be prepared using methods known in the art; see for example, the method for the preparation of 3α - tropylamine of S.Archer et al., J. Amer. Chem. Soc., 79, 4194, 1957 and the method described for the preparation of 3β-tropylamine R.Willstätter et al., Chem. Ber., 31, 1202, 1898, S.Archer et al., J.Amer. Chem. Soc., 80, 4677, 1858, and also A.Stoll et al., Helv. Chim. Acta 38, 559, 1955; further preparations of said tropylamines are described by P.Dostert et al., FR 2.449.570 (13.8.1982) C.A. 98, 126444q (1983); P. Donatsch et al., DE 33 22754 (29.12.1983); M.Langlois et al., FR 2.548.666 (11.01.1985) C.A. 103, 123757e (1985); E.A.Watts PCT WO 85 00.170 (17.01.1985) C.A. 103 123376e (1985); D.Lednicer et al., EP 147.044 (03.07.1985)

C.A. 104 1949 1986.

The preparation of the 1H-pyrrole|2,3-b|pyridine-3-carboxylic acid 7-oxide, as well as a general procedure for the preparation of 1H-pyrrole|2,3-b|pyridine 7-oxide, has been described by S.W.Schneller et al., (J.Org. Chem., 45, 4045, 1980).

The preparation of the 1H-pyrrole|2,3-b| pyridine-3-carboxylic acid as well as the ethyl ester thereof have been described by M.M. and B.L. Robinson on J. Amer. Chem. Soc., 78, 1247, 1956.

In general, 7-azaindoles and their homologues 1- or 2-substituted or 1- or 2-disubstituted, for the preparation of which see for example, R.R.Lorenz et al., J.Org. Chem., 30, 2531, 1965 and references cited therein, may be converted by a Mannich reaction into their corresponding 3-dialkylaminomethyl derivatives and then transformed in the corresponding 3-formyl-7-azaindoles which, substantially according to the above mentioned procedure of M.M. and B.L. Robinson, are converted into their corresponding esters and carboxilic acids.

More particularly it has been found that, in a halogenated solvent and in the presence of a suitable catalyst such as aluminum chloride, i.e. in Friedel-Krafts conditions, the 7-azaindoles themselves react with a trihaloacetylhalides, preferably trichloacetylchloride, to give, with a yield almost quantitative, the corresponding 3-trihaloacetyl-7-azaindoles such as, for example, 3-trichloroacetyl-1H-pyrrole[2,3-b]pyridine which, with further treatment with bases, such as potassium hydroxide, undergo the haloformic transposition into the corresponding 7-azaindolyl-3-carb xyli acids.

The following Examples are given by way of bett r illustrating the invention without limiting it.

Example 1

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide (Compound A)

In an inert gas atmosphere and under stirring, a solution of 5.4 ml of trichloroacetyl chloride in 27 ml dichloromethane is added in the course of 10 minutes to a suspension of 6.8 g aluminum chloride in 54 ml dichloromethane cooled to -78°C. It is maintained at this temperature for 15 minutes then warmed up to -40°C, maintaining under stirring for a further 45 minutes. A solution of 2 g 7-azaindole in 10 ml dichloromethane is then added, stirred for 15 minutes at -40°C and the temperature is allowed to rise to 0°C and stirring continued for a further hour. Milliliters 26 of an aqueous solution of 1N hydrochloric acid are added carefully maintaining the temperature between 0 and 15°C; after decomposition of the reagents, the phases are separated and the organic phase is washed with water and treated under strong stirring with sodium bicarbonate heptahydrate to obtain a white crystalline solid which is filtered and it gives 2.6 g 3-trichloroacetyl-1H-pyrrole-[2,3-b]pyridine melting at 260°C (with decomposition). The so obtained compound is suspended in 15 ml of a 10% potassium hydroxide aqueous solution and the suspension is kept under strong stirring until complete dissolution. By acidification of the solution to pH 3-4 with a 37% hydrochloric acid aqueous solution, 1.5 g 7-azaindolyl-3-carboxylic acid separate by precipitation, melting point 230-240°C (with decomposition).

To a solution of 1.5 g 7-azaindolyl-3-carboxylic acid in 24 ml

of a mixtur 1:1 of tetrahydrofuran:dimethylformamide, 1.29 g endo-8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylamine and 2.1 g dicyclohexylcarbodiimide are added.

The mixture is heated for 3 hours at 50°C, then it is evaporated to small volume, acidified with 2N hydrochloric acid and filtered removing the dicyclohexylurea precipitate. The filtrate is saturated with sodium chloride and after being made alkaline to pH 11 with sodium hydroxide, it is extracted with chloroform and it gives, by evaporation of the solvent and crystallization of the residue from ethyl ether, 1.24 g N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide melting at 273°C (Compound A).

Operation is carried out according to the previously described procedure and using instead of endo-8-methyl-8-azabicyclo [3.2.1]oct-3-ylamine, 1-azabicyclo[2.2.2]oct-3-yl-amine, N-(1-azabicyclo[2.2.2]oct-3-yl)-7-azaindolyl-3-carboxamide melting at 275-280°C is obtained (Compound B).

Example 2

N-(8-methyl-8-azabicyclo|3.2.1|oct-3α-yl)-7-azaindolyl-3-carboxamide 7-oxide.

To a solution of 1.5 g 7-azaindolyl-3-carboxilic acid 7-oxide in 30 ml acetonitrile, 2 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added in portions.

After 15 minutes of stirring, a solution of 1.29 g 3 α-tropylamine in 10 ml of acetonitrile is added. It is kept at room temperature for 2 hours, heated to 50°C for 2 hours, concentrated under vacuo to a third of its volume and diluted with 100 ml of water. After several extractions with ethyl acetate, the organic phases are collected together and evaporated to dryness. The residue is purified by

chromatography over silica gel ($CHCl_3$:MeOH) to give 1.12 g N-(8-methyl-8-azabicyclo[3.2.1]oct-3α-
-yl)-7-azaindolyl-3-carboxamide 7-oxide.

Example 3

N-(8-cyclopropylmethyl-8-aza-bicyclo[3.2.1]oct-3β-yl)-7-azaindolyl- 3-carboxamide.

A solution of 2.9 g N-hydroxysuccinimide in 10 ml tetrahydrofuran is added to a solution of 1.84 g 7-azaindolyl-3-carboxylic acid in 30 ml of a 1:1 tetrahydrofuran and dimethylformamide mixture cooled to 0°C and under stirring. A solution of 2.1 ml morpholynethylisonitrile in 10 tetrahydrofuran ml is dripped therein and stirring is maintained for a further two hours to room temperature. It is diluted with 5 volumes of water, tetrahydrofuran is removed by evaporation under vacuum, it is acidified to pH 3-4 with a potassium acid sulphate aqueous solution and extracted with ethyl acetate. From the collected together organic extracts, by evaporation of the solvent, 2.6 g 7-azaindolyl-3-carboxylic acid succinimide ester crystallizes.

Grams 1.02 of the so obtained succinimide ester are dissolved at room temperature and in argon atmosphere in 7.5 ml acetonitrile and to the solution 5 ml of a solution of 0.75 g 3β-amino-8-cyclopropylmethyl-8-azabicyclo[3.2.1]octane in 0.5 ml acetonitrile are added. After 8 hours, the mixture is concentrated under vacuum to small volume and diluted with a sodium bicarbonate saturated solution until a slight alkaline pH. It is extracted four times with 20 ml each of ethyl acetate and from the collected together extracts, after evaporation of the solvent and crystallization from ethyl

ether, 1.5 g of N-(8-cyclopropylmethyl-8-aza-bicyclo[3.2.1]oct-3ß-yl)-7-aza-indolyl-3-carboxiamide are obtained.

In a similar manner by reaction with the suitable 3-amino-8-azabicyclo[3.2.1] octane are obtained:

- N-(8-cyclopropylmethyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-formyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-tert-butoxycarbonyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-phenylethyl-8-azabicyclo[3.2.1]oct-3∝-yl)-7-azaindolyl-3-carboxyamide;
- N-(8-benzyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-cyclohexylmethyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-cyclopentylmethyl-8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide;
- N-(8-ethyl-8-azabicyclo[3.2.1]oct-3 ∝-yl)-7-azaindolyl-3-carboxyamide;
- N-(8-isopropyl-8-azabicyclo[3.2.1]oct-3∝-yl)-7-azaindolyl-3-carboxyamide.

Example 4

N-(8-azabicyclo[3.2.1]oct-3 ∝ -yl)-7-azaindolyl-3-carboxyamide tri-fluoroacetate.

A solution of 0.3 g N-(8-tert-butoxycarbonyl-8-azabicyclo[3.2.1] oct-3∝-yl)-7-azaindolyl-3-carboxyamide in 2 ml of dichloromethane and 2 ml of trifluoroacetic acid is maintained for 8 hours at room temperature then the reaction

mixture is evaporated to dryness under vacuum and the residue, crystallized from ethyl ether:hexane, and it gives the trifluoro acetate of N-(8-azabicyclo[3.2.1]oct-3$\alpha$-yl)-7-azaindolyl-3-carboxyamide.

Benzoyl N-quinuclidinylamides and N-tropylamides and analogous amides of aryl- and heteroarylcarboxylic acids represent compounds which in the last decade were the object of wide researches having as aim the identification and the functional characterization of the subtypes of the serotonin (5-HT) receptor and the realization of ligands having high bond affinity and high receptor specificity. Substances belonging to the same family of compounds have resulted clinically effective in the control of the emesys induced by antitumoral chemotherapy, a pharmacological event which was supposed to be modulated by $5\text{-HT}_3$ receptors in the area postrema. Lastly there are pharmacological indications which make believe that these substances because they are $5\text{-HT}_3$ antagonists, may be useful in correcting affections of the central nervous system, such as, for example, schizophrenia, anxiety or the loss of memory, since $5\text{-HT}_3$ receptors also seem to modulate the cholinergic neurons.

Specific examples of $5\text{-HT}_3$ antagonists are, for example, Ondasetron, BRL 24682 or N-(endo-8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-2-methoxy-4-amino-5-chlorobenzamide, ICS-205-930 or (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)indolyl-3-carboxylate.

More recently, both quinuclidyl- and tropyl-amides of the 7-methyl- 8-azaindolyl-3-carboxylic acid(T.Higashino et al., Toyo Jozo Co., EP 483 836 (06.05.1992), C.A. 117 171436K and 2-methylimidazo|1,2-a| pyridin-3-carb xylic acid (K.Nitta t

al., Mitsubishi Kasei Corp. JP 01258679 (16.10.1989), C.A. 112 178986v) have been described as 5-$HT_3$ antagonists and therefore are useful as antiemetic, in the prevention of nausea by cis-Platin and, more in general, as antiserotoninergic drugs to be used for the treatment of the migraine and anxiety.

The amides of the 7-azaindol-3-carboxylic acid (F.D.King, Beecham Group, EP 254 584 (27.01.1988) C.A. 109 93018u) have also been described as 5-$HT_3$ -antagonists. Lastly, more recently, M.Kato et al. (Fujisawa Pharmac., JP 04021681 (24.01.1991) C.A. 116 255499a) describe pyrrolpyridinecarboxyamides of azabicycloalkylamines as typical 5-$HT_3$ antagonists with particular mention to the amides of 3-amino-8-methylazabicyclo[3.2.1]octane with 1-methyl and 1-ethyl-7-azaindolyl-3-carboxylic acids.

Compounds A and Compounds B of the present invention, which are examples of endo-tropyl and quinuclidylamide of 7-azaindolyl-3-carboxylic acid respectively have been studied "in vitro" for their interaction with the 5-$HT_1$, 5-$HT_2$ and 5-$HT_3$ receptors.

Table I

| Binding Test: | 5-$HT_1$ | 5-$HT_2$ | 5-$HT_3$ |
|---|---|---|---|
| | % of inhibition at 3.6 $10^{-5}$ M | | $IC_{50}$ M |
| Ondasetron | 7.6 | 21.7 | 3 $10^{-9}$ |
| Compound A (7-azaindolylcarboxy tropylamide) | 0.0 | 8.6 | 3 $10^{-6}$ |
| Compound B (7-azaindolylcarboxy quinu lidylamid ) | 37.0 | 3.9 | 3 $10^{-7}$ |

From the above study a first indication of an atypic behaviour of 7-azaindolyl-3-carboxylic acid tropylamides when compared to the corresponding quinuclidylamid surprisingly appeared.

The interaction of Compounds A and B with other receptors ($\alpha_1$, $\alpha_2$, benzodiazepine (o bzd), GABA A, $\sigma$ ) in comparison to the typical 5-$HT_3$ antagonist Ondastron and BRL 24682 has been studied and for each case the displacement % of the single selective ligand from the corresponding receptor at concentration $10^{-5}$ M of the compounds under examination, has been evaluated.

Table II

| Dispacement percentage | | | | | |
|---|---|---|---|---|---|
| Receptors: | $\alpha_1$ | $\alpha_2$ | bdz | Gaba A | $\sigma$ |
| Ondasetron | 72 | 30 | * | 38 | 45 |
| BRL 24682 | 28 | 16 | 98 | 89 | 0 |
| Compound A | 13 | * | * | 83 | 70 |
| Compound B | 7 | * | * | 6.7 | 26 |

* not active: no capacity of displacement of the ligand at a conc. $10^{-5}$ M.

The disparity in behaviour between 7-azaindolyl-3-carboxylic acid quinuclidyl- and tropyl-amides results even more evident from the above-listed data. 7-Azaindolylcarboxamide (Compound A) shows a very weak interaction with 5-$HT_3$ receptors: 1,000 times lower than that of Ondasetron, which is a typical 5-$HT_3$ antagonist, and logarithmically lower than that of Compound B. Compound A itself shows surprisingly an unusual ability of a double interaction, apparently selective, towards GABA A and $\sigma$ receptors, which ability is definitely weaker absent in the

corresponding quinuclidylamide and, to the contrary, it seems aspecific in 5-$HT_3$ antagonist Ondasetron.

As to the other 5-$HT_3$ antagonist, BRL 24682, it is evident its high interaction with the benzodiazepine and GABA A receptors, and its complete lacking of interaction with the receptors, thus allowing to exclude that the selective interaction of 7-azaindolylcarboxytropylamide (Compound A) with GABA A and $\sigma$ receptors be a characteristic generally present in potential 5-$HT_3$ antagonists, or, at least in substances so defined on the basis of a simple chemical structure analogy.

Besides these differences "in vitro" on the receptor behaviour great differences has been evidenced "in vivo" in the tussive stimulus inhibition provoked by inhalation of irritant citric acid as well as capsaicine aqueous solutions.

The compounds have been tested in guinea pigs in comparison to codeine, used as standard compound, at the single dose of 100 mg/kg according to the technique of Charlier et al., (Arch. Int. Pharmacodyn., 134, 306, 1961) which has been slightly modified.

The percent reduction evaluated in the number of short coughs after administration of the compound under examination taken in comparison to the number of short coughs observed in each of the animals to which the compound was administered, have been noted.

For each of the compounds under examination it has been also tested the effect on the increase of the sleeping time induced by barbiturates. The test was carried out on mice by oral administration of a single dose of 100 mg/kg of the compound. The data obtained are listed in the following Table III.

Table III

| | % INHIBITION of the coughing stimulus by: | | % |
|---|---|---|---|
| | ac. citric | capsaicin | sleeping time increase |
| Ondasetron | 30.5 | 50.5 | - 8* |
| BRL 24682 | 44.1 | n.d. | + 34.8 |
| Compound A (7-azaindolylcarboxy tropylamide) | 61.7 | 76.30 | - 28.9 |
| Compound B (7-azaindolylcarboxy quinuclidylamide) | 46.0 | 21.0 | - 7 |
| Codeine | 63.2 | 58.4 | + 106.4 |

* at the dose of 10 mg/kg n.d.: not determinable

In a successive study, carried out at different doses, using as comparison compounds typical antitussive compounds commonly used in therapy, either having a central effect, i.e. codeine, or having a peripheral effect, i.e. levodropropizine, it has been observed that the protecting antitussive effect of 7-azaindolylcarboxytropylamine (Compound A) depends on the dose administered. For these compounds as well as for the most interesting reference compounds the dose inhibiting 50% of the short coughs ($ID_{50}$) induced either by citric acid or capsaicine has been determined.

Table IV

| | $ID_{50}$ in mg/kg os (95% confidence) Coughing stimulus | | |
|---|---|---|---|
| | Ac. citric | Capsaicin | 2N $H_2SO_4$ |

| | | | |
|---|---|---|---|
| Levodropropyzina | 151 (126-180) | 145 (84-252) | 265 (168-240) |
| Codein | 65 (57-74) | 74 (52)107) | 102 (55-190) |
| Ondasetron | 209 (126-349) | 97 (30-261) | - - - |
| Compound A | 57 (41-80.5) | 51 (33-77) | - - - |

- - - not tested

In both pharmacological tests only 7-azaindolyl-3-carboxy-endo-N-tropylamide (Compound A) showed to be effective. Compound A proved to be at least equiactive as codeine, and advantageously in respect to the latter, it does not show any increase of the sleeping time induced by barbiturates.

It is assumed that Capsaicine releases substance P from the peripheral nerve endings of the sensitive fibers C and determines the necrosis of the same. It is known that capsaicine administration provokes the formation of an exudate (extra vasation by capsaicine) which can be evaluated by concomitant Evans bleu administration.

Solely Compound A and not Ondasetron has been found to give a 42% protection (in comparison with non-treated animals) from capsaicine extravasation when the compounds are administered at 10 mg/kg dosage by intraperitoneal route. A similar protection has been observed after cis-2-benzhydryl-1-azabicyclo-[2.2.2]octane-3-(2-methoxybenzyl amine (CP 96 345, a non-peptide antagonist of substance P) administration at 10 mg/kg i.p.. It is worth to underline that the same substance CP 96 345 has been found to protect guinea pigs from cough induced by capsaicin being a 26 and 42% short cough inhibition evaluated after intraperitoneal

administration of 10 and 40 mg/kg respectively.

The compounds of the invention can be then therapeutically employed as antitussive agents without the limitation of the opiate ligand antitussive drugs like as codeine. They are useful in the treatment of coughs of different origin particularly against tussive manifestations mediated by substance P.

More particularly the compounds of the present invention are helpful to prevent nocturnal cough stimuli, due to the administration of ACE-inhibitors, widely used in the hypertension treatments of which conditions the nocturnal cough represents a side effect which is hard to cure.

The compounds of the invention are also useful in the treatment of inflammatory conditions and more generally of those pathological conditions in which substance P and other neuropeptides have a conclusive etiological part and moreover in asthmatic conditions and pain of neurological origin.

The compounds of the invention may be administered by oral, sublingual, endovenous, subcutaneous, intramuscular, rectal route and by inhalation. The preferred doses vary from about 0.05 to about 15 mg/kg/die, depending on the conditions, weight, age of the patient and on the administration route. Higher dosages of the compounds of the invention, even for a prolonged period of time, have no contraindication because of their very low toxicity. Compound A $LD_{50}$ in mice is 1 g/kg by oral route.

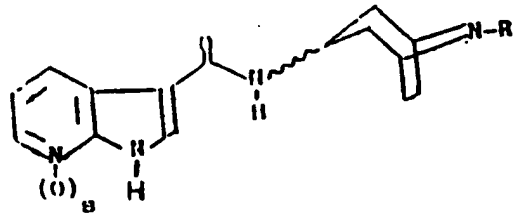
The compounds of the invention may be therapeutically used in most of the pharmaceutical preparations, using conventional techniques and excipients as are described in "Remington's Pharmaceutical Sciences Handbook" Hack Publ.Co.New York, USA.

These compositions include capsules, tablets, drinkable solutions, suppositories, vials for parenteral route and by inhalation, systems with controlled release and similar.

5

Claims

1. Tropyl 7-azaindol-3-ylcarboxyamides of formula (I)



(I)

wherein the symbol ~ indicates that compounds (I) may have the configuration exo(or ß-) or endo(or α-) and

R represents a hydrogen atom; a saturated linear or branched $C_1$-$C_4$ alkyl; a $C_7$-$C_9$ arylalkyl; a $-(CH_2)_n-(C_3-C_7)$ cycloalkyl group wherein n is an number between 0 and 4; a $C_1$-$C_{12}$ acyl group,

s repreents 0 or 1

and the corresponding non-toxic pharmaceutically acceptable acid addition salts.

2. N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-azaindolyl-3-carboxamide.

3. A pharmaceutical composition having antitussive activity which contains a therapeutically effective quantity of a compound according to claims 1 and 2 in mixture with suitable pharmaceutically acceptable diluents.

4. A pharmaceutical compositon useful for the treatment of asthmatic conditions and neurological origin algesia wich contains a therapeutically effective quantity of a compound according to claims 1 and 2 in mixture with suitable pharmaceutically acceptable diluents.

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# INTERNATIONAL SEARCH REPORT

b ational Application No
PCT/IB 94/00234

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D519/00 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992, Columbus, Ohio, US; abstract no. 255499a, KATO, MASAYUKI ET AL. 'Preparation of pyrrolopyridine derivatives as 5-HT antagonists.' see abstract * RN 141650-61-5, -60-4, -59-1, -58-0, -56-8 * & JP,A,9 221 681 (FUJISAWA PHARMACEUTICAL CO.) | 1 |
| A | EP,A,0 504 679 (G.D. SEARLE & CO.) 23 September 1992 see claims | 1 |

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 September 1994 | - 3. 10. 94 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+ 31-70) 340-3016 | Van Bijlen, H |

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 94/00234

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,A | EP,A,0 581 165 (DOMPE' FARMACEUTICI S.P.A.) 2 February 1994<br>see claims | 1,3 |

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Information on patent family members

| International Application No |
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| PCT/IB 94/00234 |

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
| --- | --- | --- | --- | --- |
| JP-A-9221681 | | NONE | | |
| EP-A-0504679 | 23-09-92 | US-A- | 5260303 | 09-11-93 |
| | | AU-A- | 1572892 | 06-10-92 |
| | | EP-A- | 0530353 | 10-03-93 |
| | | JP-T- | 6500124 | 06-01-94 |
| | | WO-A- | 9215593 | 17-09-92 |
| EP-A-0581165 | 02-02-94 | NONE | | |